



Indiana
Department
of
Health

TREATMENT UPDATES

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Disclosures

- Medical consultant, TB Program
Indiana Department of Health
- Owner of a 38 consecutive streak of negative TB screening tests!
- Genuine Iowa farm boy
- Grandfather of Avery Lynn

Objectives

- Review TB impact on world health
- Overview of LTBI treatments
 - New regimens and supply challenges
- Overview of TB treatments
 - First new regimens in decades have arrived

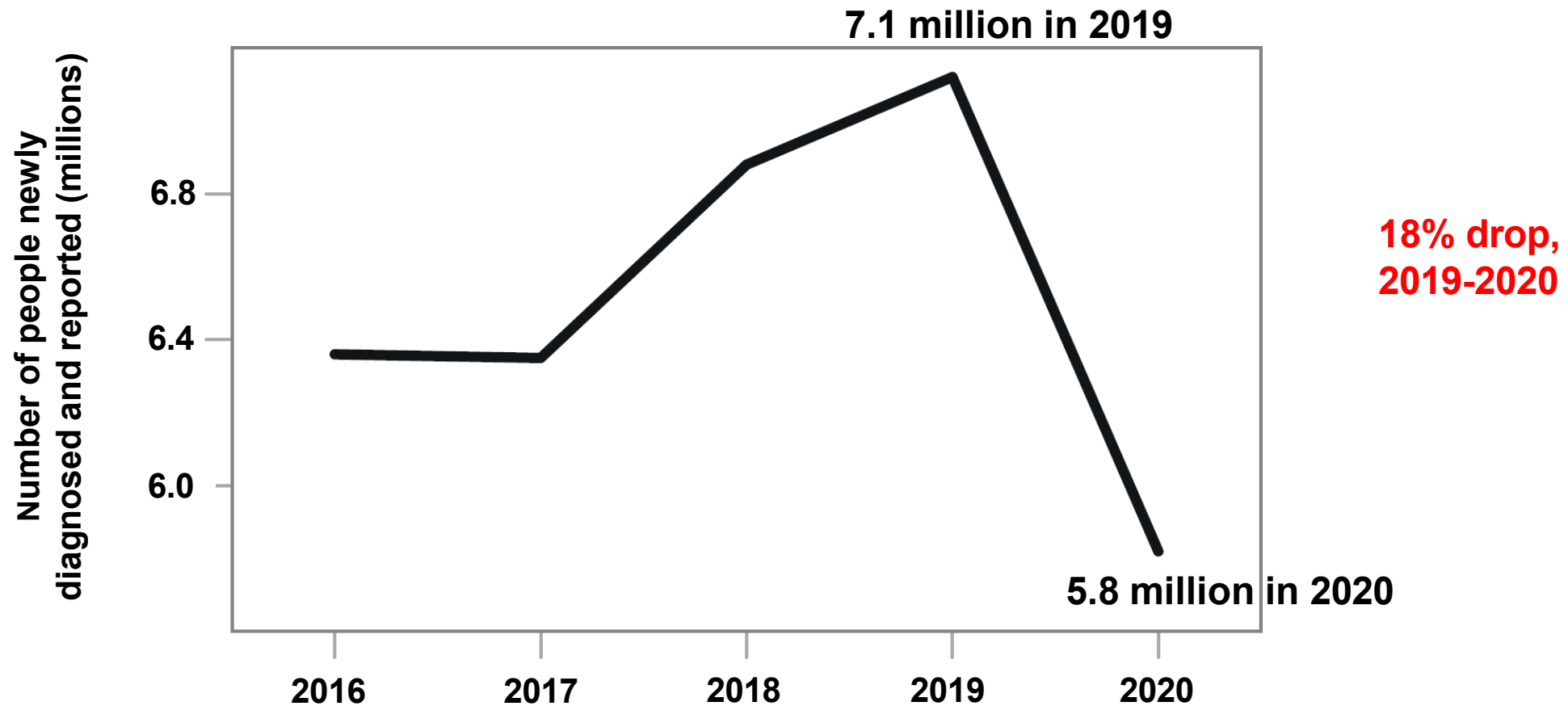
Global/U.S. TB Burden, 2020

- An estimated 10 million new TB disease cases
- 1.5 million deaths due to TB disease (1.2, '19)
 - With 0.21 million deaths from TB among people living with HIV (0.20 last year)
- TB incidence is falling at about 2% per year
- Estimated up to 13 million persons in U.S. TB infected
- Incidence rate of U.S. cases, 2.2/100,000, total of 7,174

Sources: WHO Global Tuberculosis Report 2021,
<https://www.who.int/news-room/fact-sheets/detail/tuberculosis>
CDC: <https://www.cdc.gov/tb/statistics/default.htm>

Most Immediately Obvious Impact of COVID-related Disruptions

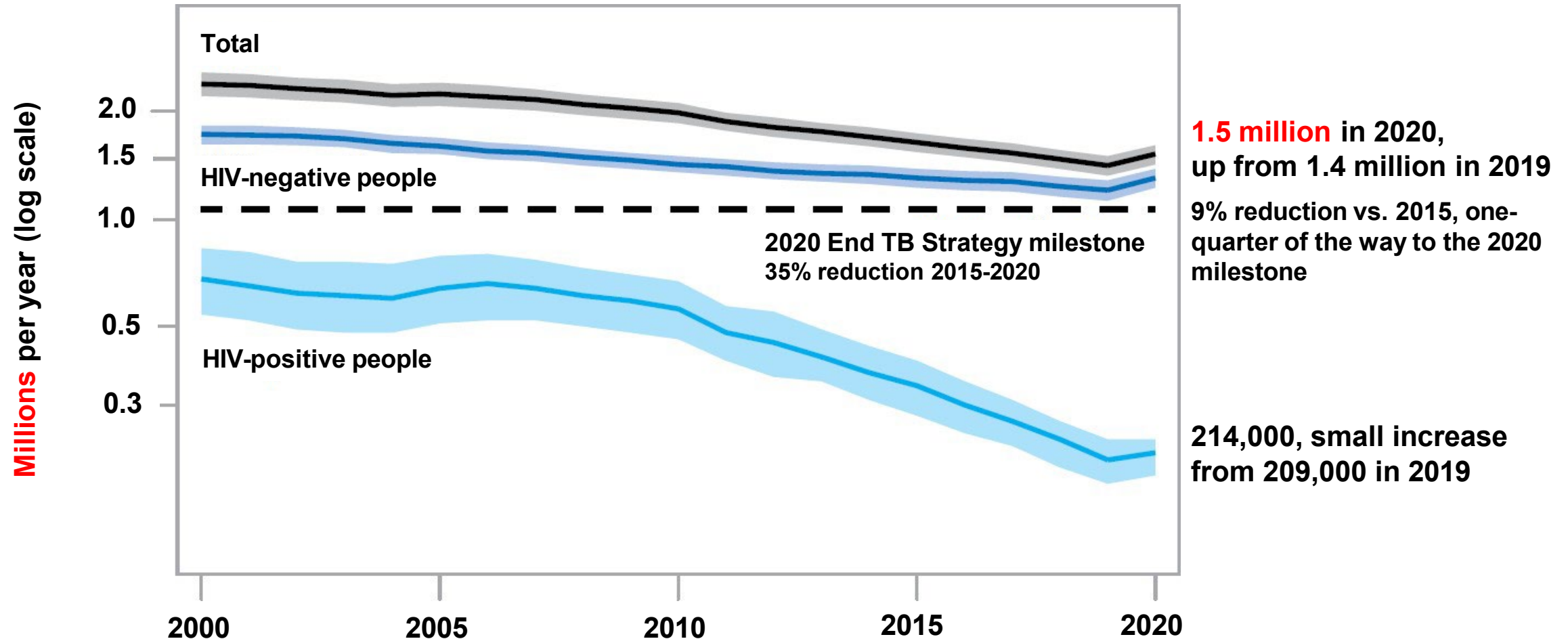
Big global drop in number of newly diagnosed/reported TB cases



Global Number of TB Deaths Increased in 2020

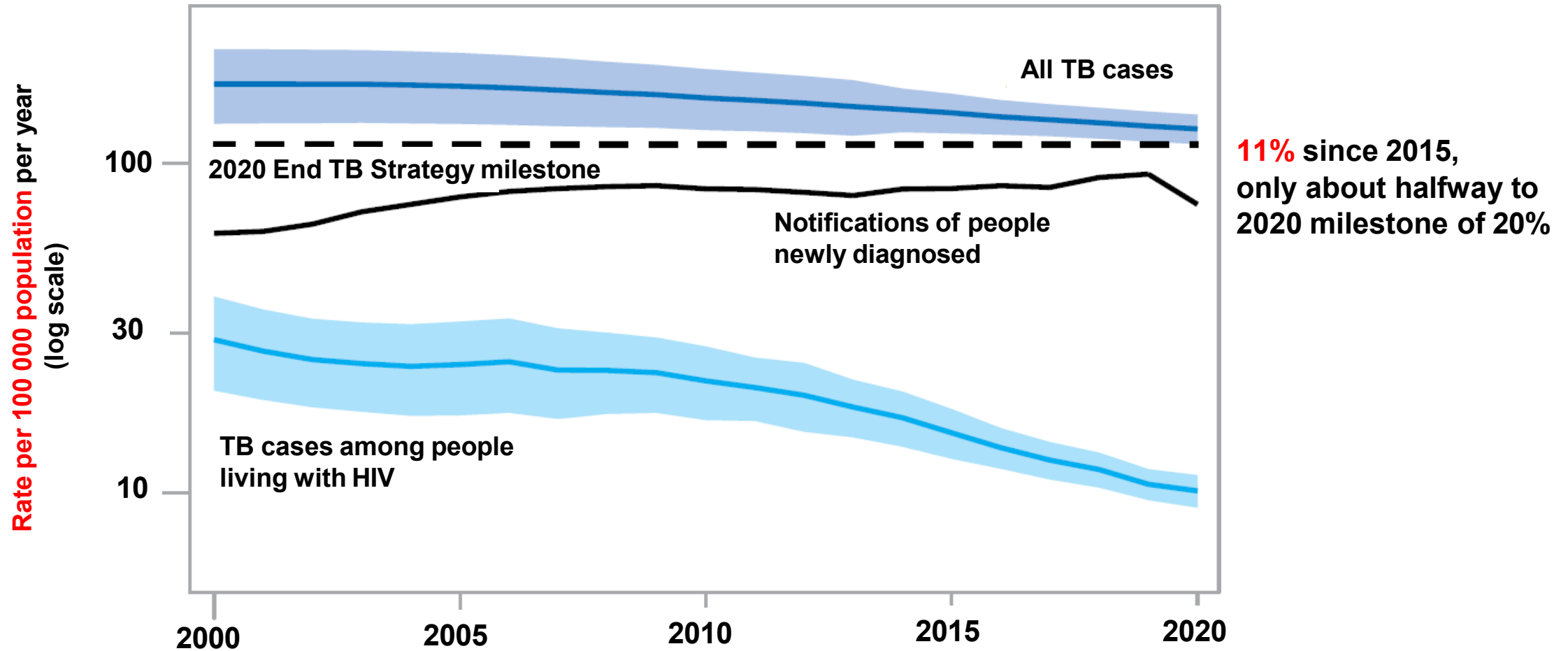
first year-on-year increase since 2005, back to the level of 2017

TB second only to COVID-19 as cause of death from single infectious agent

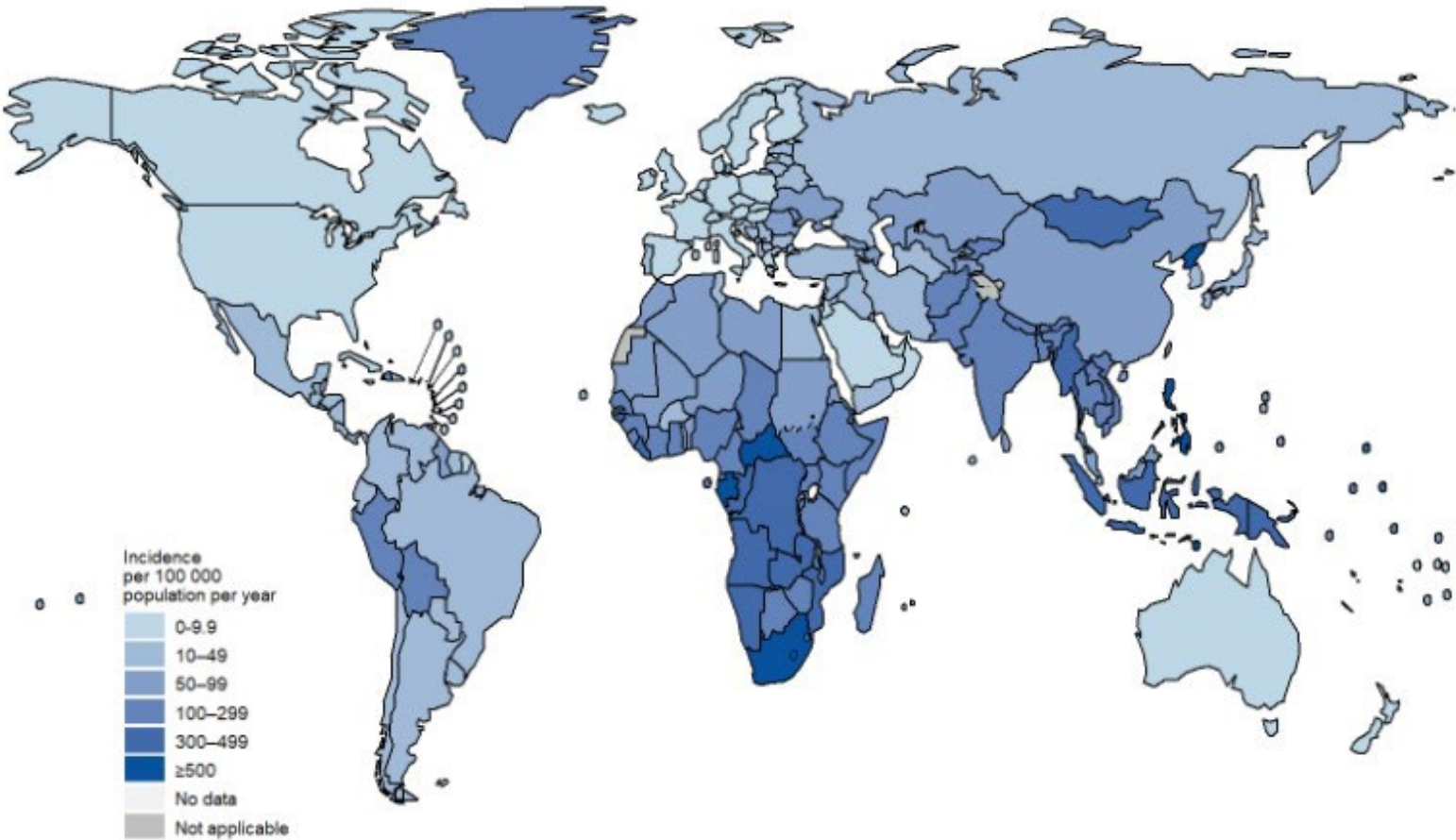


Global Decline in TB Incidence Slowed in 2020

1.9% overall drop in 2019-2020, down from 2.3% 2018-2019

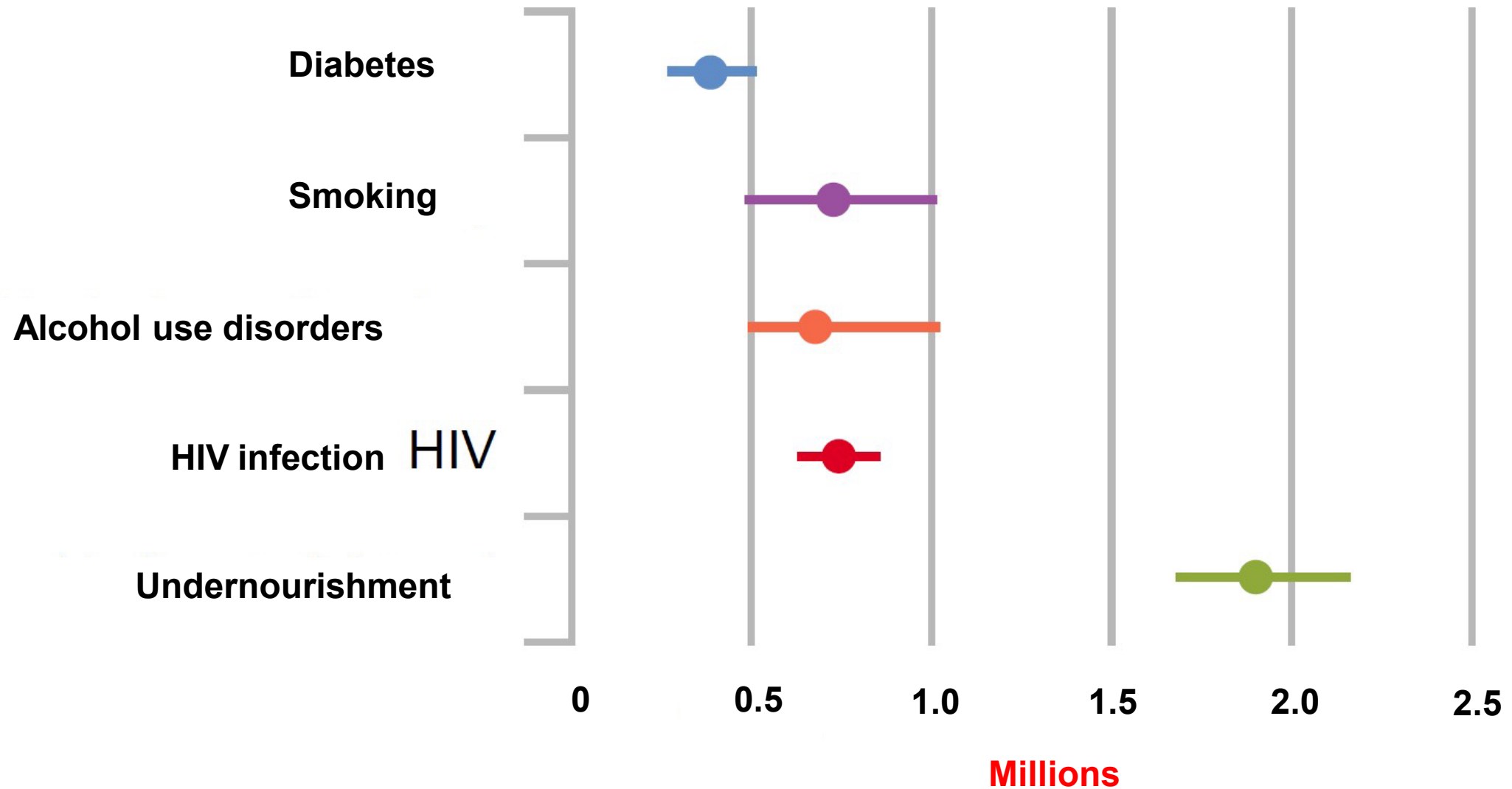


Estimated World TB Incidence Rates, 2020



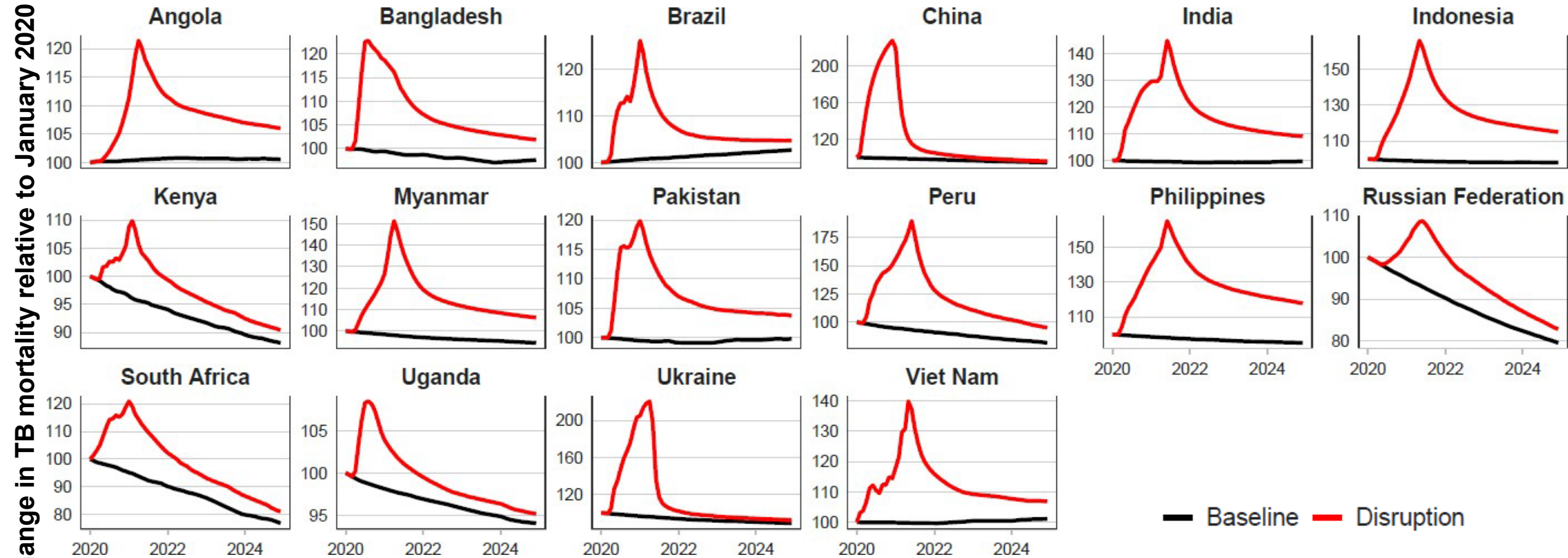
TB Determinants

Estimates of TB cases attributable to 5 risk factors in 2020



Much Worse Impacts Forecast in 2021 and 2022

a) TB deaths

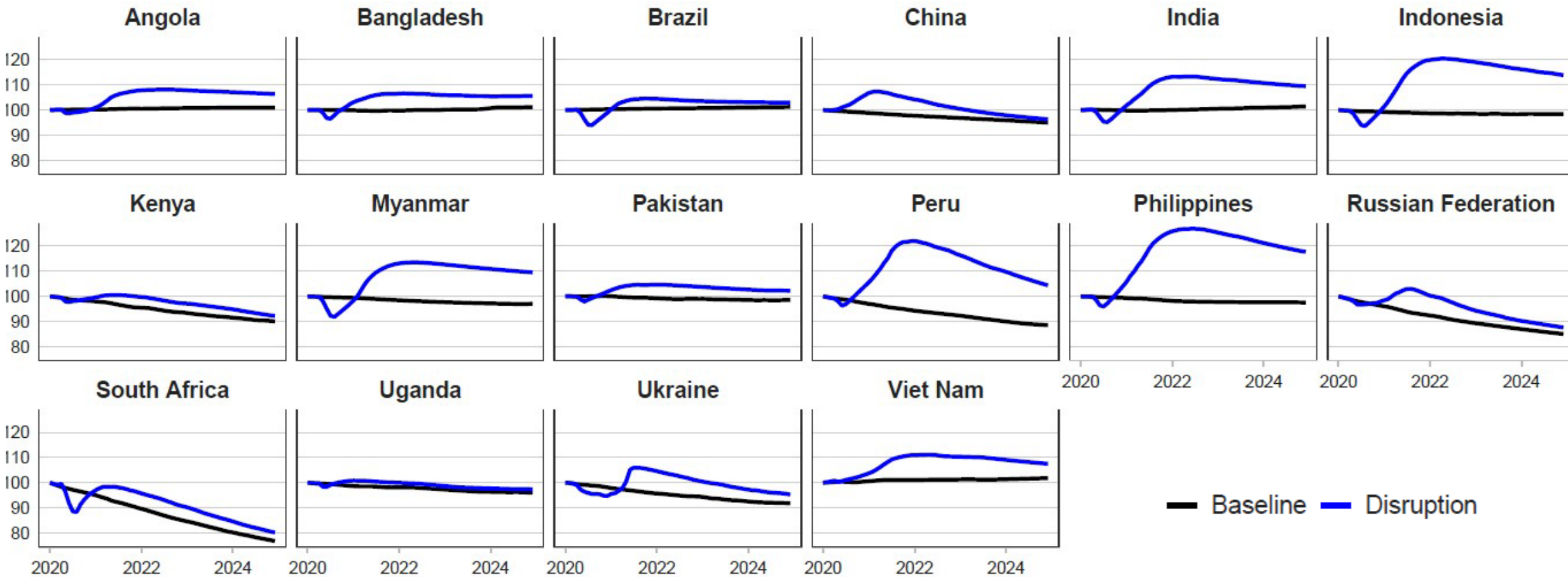


Impact of COVID-related disruptions on TB deaths **likely to peak in 2021**, could persist for much longer

Much Worse Impacts Forecast in 2021 and 2022

b) TB incidence

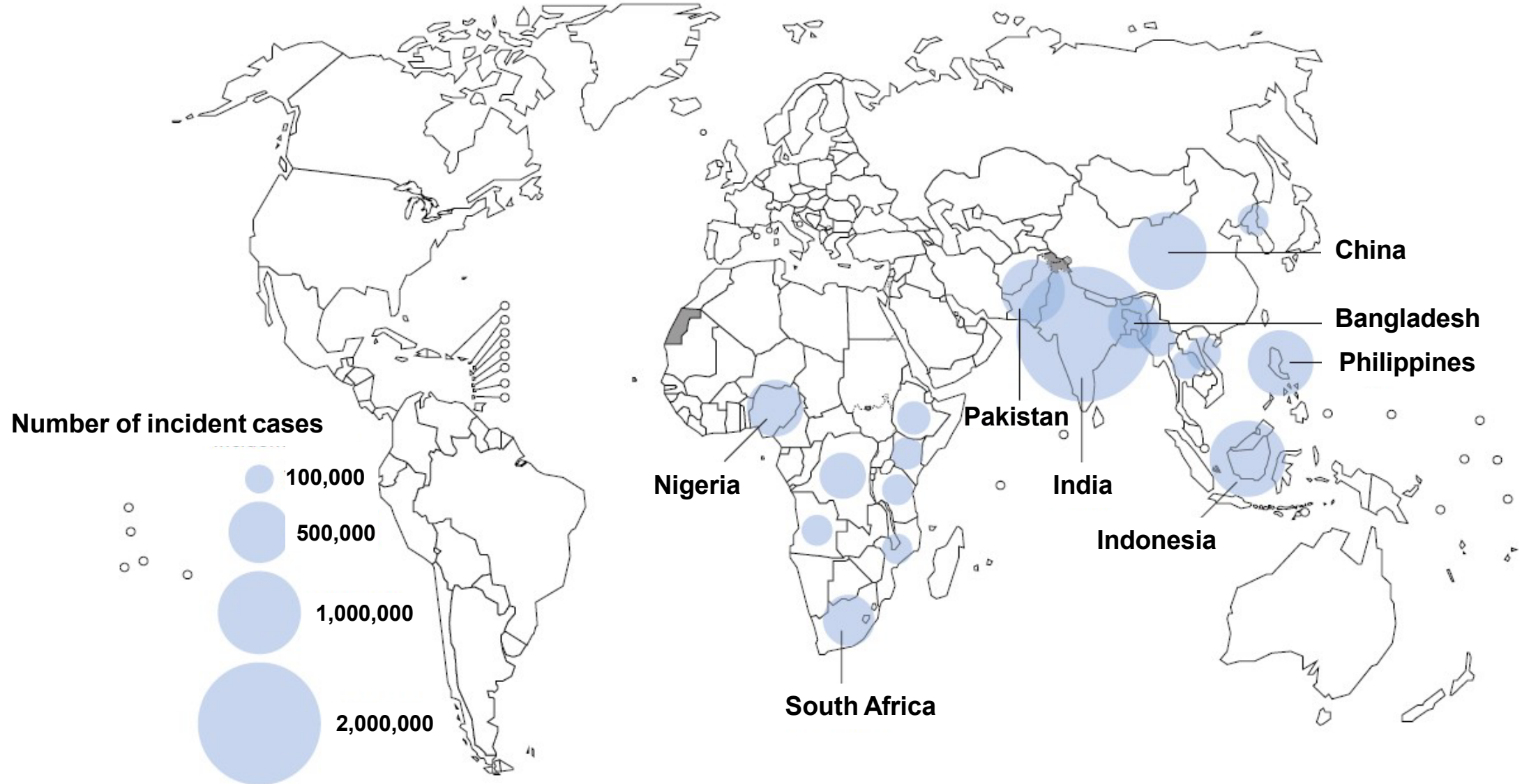
% change in TB incidence relative to January 2020



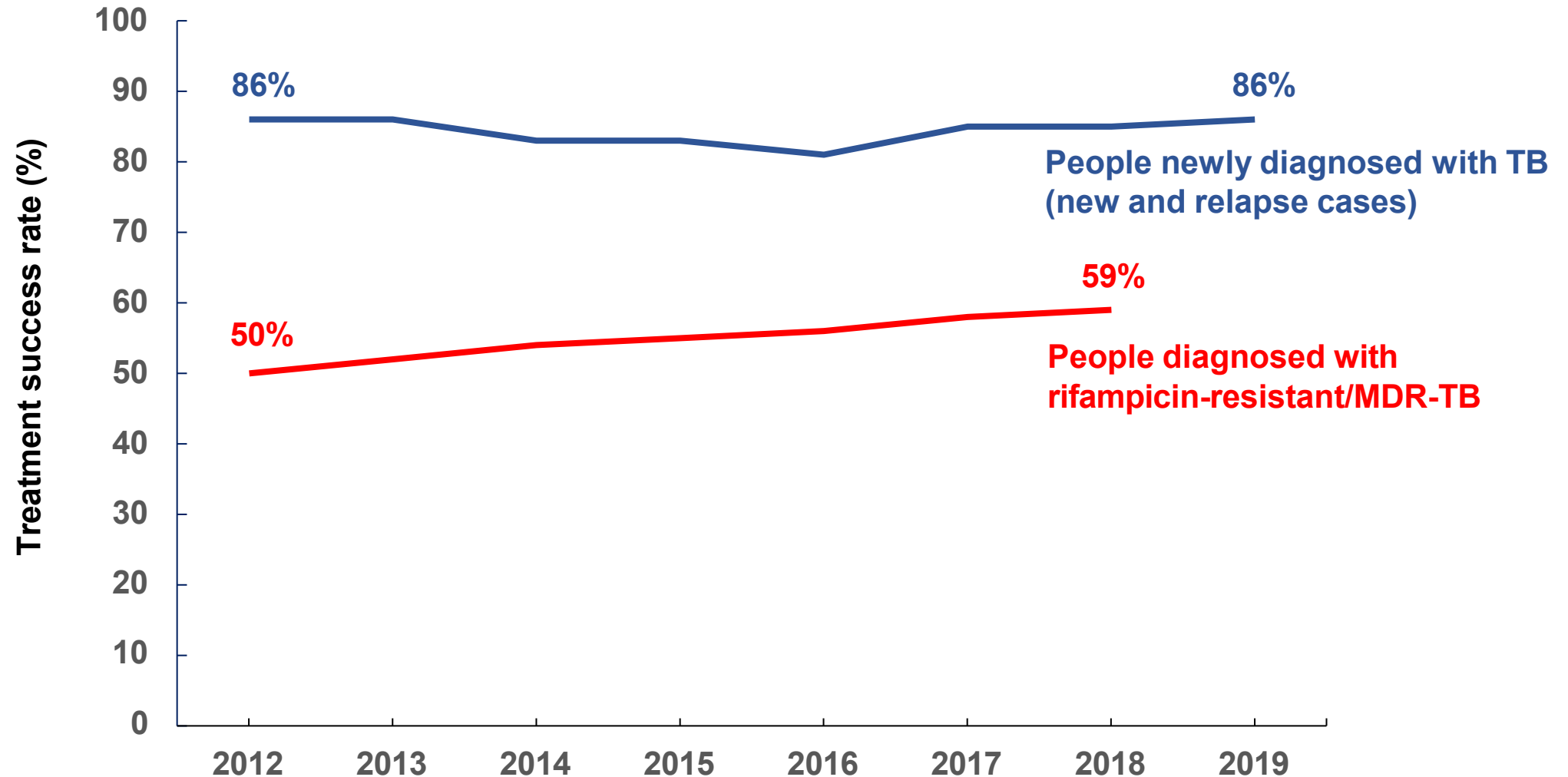
Impact of COVID-related disruptions on TB incidence **likely to peak in 2022**, could persist for much longer

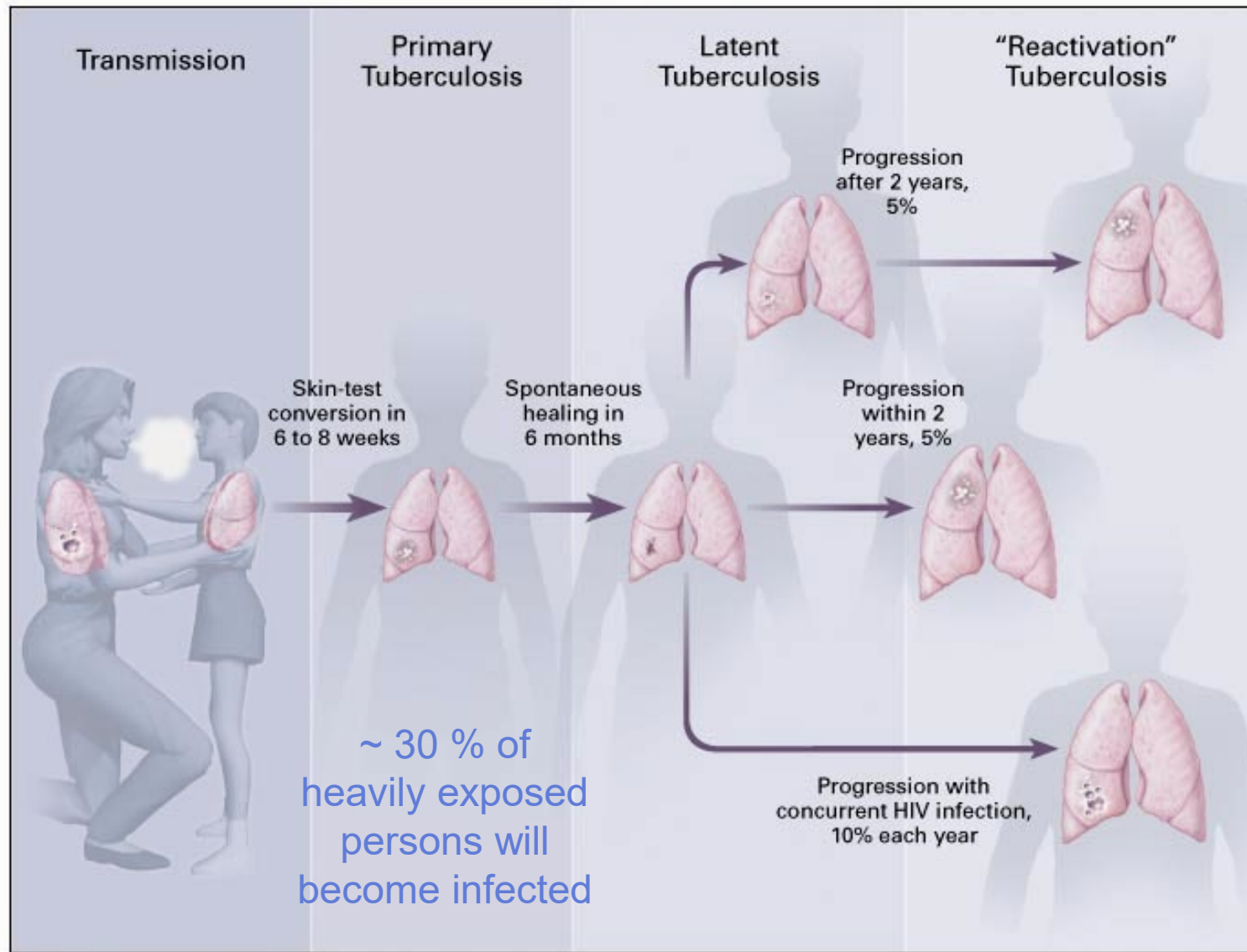
8 Countries, Two-thirds of Global Cases in 2020

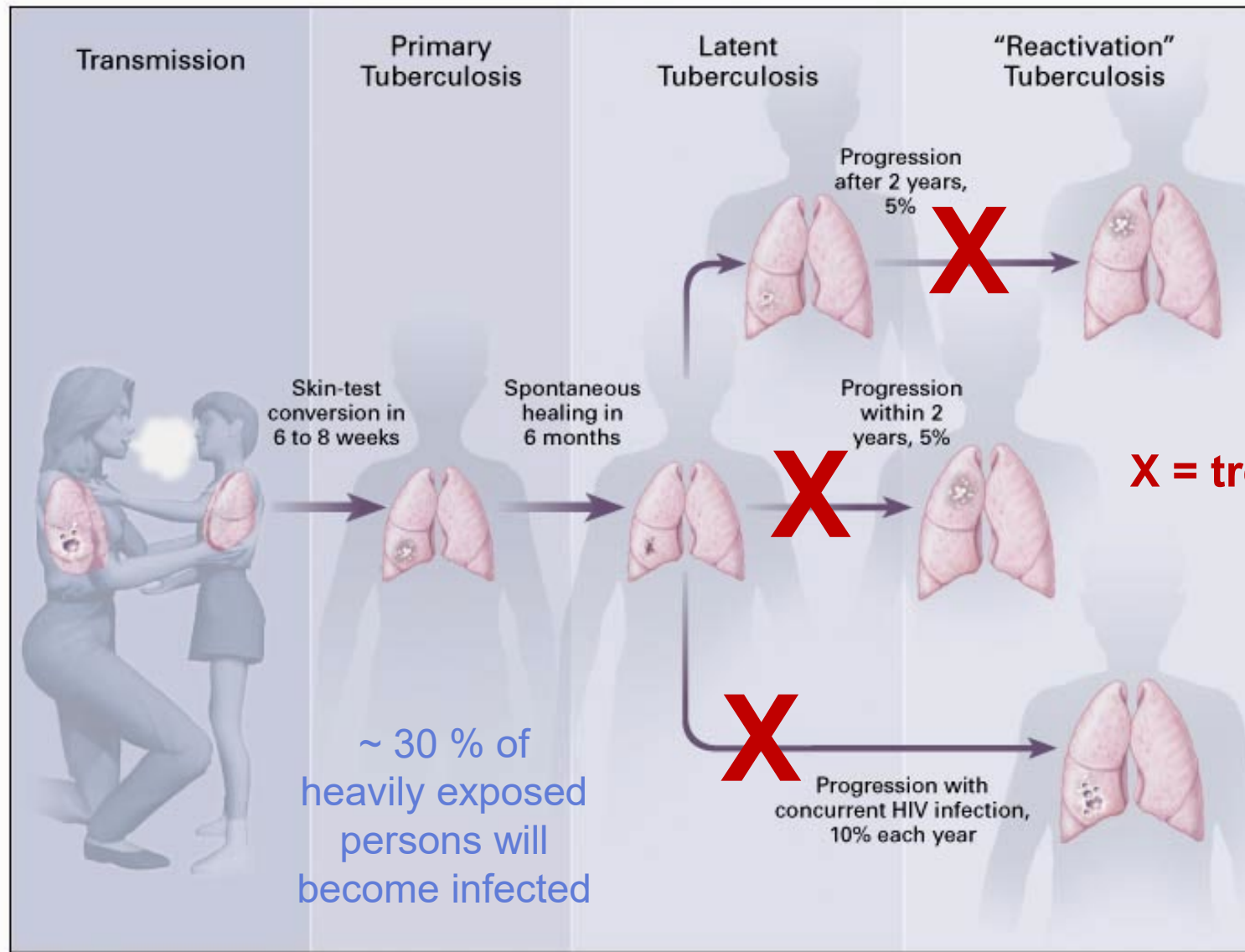
86% in 30 high TB burden countries



Treatment Outcomes







LTBI Treatment Regimens

- An optimal LTBI treatment is minimally toxic and as short as possible to enhance completion rates.
- Preferred regimens:
 - 3 months once weekly isoniazid plus rifapentine (3HP)
 - 4 months daily rifampin alone (4R)
 - 3 months daily isoniazid plus rifampin (3HR)
- Alternative regimen:
 - 6–9 months of isoniazid monotherapy

Stagg, Zenner, et al. 2014. Treatment of Latent Tuberculosis Infection: A Network Meta-analysis. *Ann Intern Med.* 2014;161(6):419-428

Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep* 2020;69(No. RR-1):1–11.

<https://www.cdc.gov/tb/topic/treatment/pdf/LTBITreatmentRegimens.pdf>

TB Disease Treatment Regimens

For a number of years, the main treatment regimen for drug-susceptible TB disease has been a 6- to 9-month RIPE regimen consisting of:

- Rifampin (RIF),
- Isoniazid (INH),
- Pyrazinamide (PZA), and
- Ethambutol (EMB)

RIPE regimens for treating TB disease traditionally feature:

- Intensive phase of 4 drugs for 2 months
- Followed by a continuation phase of 2 or more drugs for 4 or 7 months
- Total of 6 to 9 months for treatment depending on severity and response

RIPE

TB Disease Treatment Regimen Table

Intensive Phase				Continuation Phase						
Drugs ^a	Duration	Frequency ^b		Drugs	Duration	Frequency ^{b,c}		Total Doses	Comments ^{c,d,e,f}	Regimen Effectiveness
INH RIF PZA EMB	8 weeks	7 days/week for 56 doses	5 days/week for 40 doses	INH RIF	18 weeks	7 days/week for 126 doses	5 days/week for 90 doses	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	Greater
INH RIF PZA EMB	8 weeks	7 days/week for 56 doses	5 days/week for 40 doses	INH RIF	18 weeks	3 times weekly for 54 doses		110 to 94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
INH RIF PZA EMB	8 weeks	3 times weekly for 24 doses		INH RIF	18 weeks	3 times weekly for 54 doses		78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
INH RIF PZA EMB	8 weeks	7 days/week for 14 doses then twice weekly for 12 doses ^g		INH RIF	18 weeks	2 times weekly for 36 doses		62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed then therapy is equivalent to once weekly, which is inferior.	
<p>Do Not Use!!! - Increased failure rate with twice weekly therapy of TB disease</p>										

Source: <https://www.cdc.gov/tb/topic/treatment/tbdisease.htm>



Abbreviations: INH = isoniazid; RIF = rifampin; PZA = pyrazinamide; EMB = ethambutol; HIV = human immunodeficiency virus

The New Frontier! Study 31 Background

- Reducing the duration for treating TB has been a longstanding goal:
 - Shorter regimens cure patients faster and have the potential to reduce treatment costs, improve patient quality of life and increase completion of therapy.
- Key study question:
 - Does high-dose daily rifapentine, with or without moxifloxacin, allow treatment shortening from 6 to 4 months for drug-susceptible TB?

34 Clinical Research Sites, 13 Countries, 4 Continents



Adapted from TB Centers of Excellence and the CDC presentation: Considerations for the New Four-Month Rifapentine-Moxifloxacin Regimen for Drug-Susceptible TB in the U.S. September 21, 2021.

Study 31 Results

On **May 5, 2021**, CDC's Tuberculosis Trials Consortium and the National Institutes of Health-sponsored AIDS Clinical Trials Group published results from the randomized controlled trial—Study 31—in the [New England Journal of Medicine](#).

- The study results indicated that a 4-month regimen containing rifapentine (RPT), moxifloxacin (MOX), isoniazid (INH) and pyrazinamide (PZA) **was as effective** as the standard 6-month RIPE regimen for TB treatment.

This is the first new treatment regimen for drug-susceptible TB disease in almost 40 years!

CDC Interim Guidance

In February 2022, the [CDC issued interim guidance](#) on the use of the 4-month Rifapentine-Moxifloxacin regimen for the treatment of drug-susceptible pulmonary TB.



Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

Wendy Carr, PhD¹; Ekaterina Kurbatova, MD¹; Angela Starks, PhD¹; Neela Goswami, MD¹; Lecanna Allen, MPH¹; Carla Winston, PhD¹

Four-month Rifapentine-Moxifloxacin TB Treatment Regimen

The 4-month TB treatment regimen consists of:

- High-dose daily rifapentine (RPT) with
- Moxifloxacin (MOX),
- Isoniazid (INH), and
- Pyrazinamide (PZA)

The 4-month rifapentine-moxifloxacin regimen has an intensive phase of 4 drugs for 2 months, followed by a continuation phase of 3 drugs for 2 months and 1 week (total 17 weeks for treatment).

Four-month TB Treatment Regimen Table – Study 31

Intensive Phase			Continuation Phase					
Drugs	Duration ^a	Frequency ^b	Drugs	Duration ^c	Frequency ^b	Total Doses	Comments ^{d,e}	Regimen Effectiveness
RPT MOX INH PZA	8 weeks	7 days/week for 56 doses	RPT MOX INH	9 weeks	7 days/week for 63 doses	119	Recommended for people ages 12 and older with body weight at or above 40 kg, with pulmonary TB caused by organisms that are not known or suspected to be drug-resistant, and who have no contraindications to this regimen.	The 4-month rifapentine-moxifloxacin TB treatment regimen is as effective as (noninferior to) the standard daily 6-month regimen in curing drug-susceptible TB disease.

Abbreviations: RPT= rifapentine; MOX= Moxifloxacin; INH = isoniazid; PZA = pyrazinamide



Source: <https://www.cdc.gov/tb/topic/treatment/tbdisease.htm>

Considerations for Specific Groups of People with TB Disease

CDC **recommends** the 4-month rifapentine-moxifloxacin regimen **as an option** for treating **pulmonary TB disease** caused by organisms that are not known or suspected to be drug-resistant for:

- People who are 12 years and older
- People with a body weight at or above 40 kg
- People with HIV with CD4 counts at or above 100 cells/microliter (μL), who are receiving or planning to start efavirenz as part of their ART regimen in the absence of any other known drug-drug interactions between antit-TB and anti-HIV meds
- People who have no contraindications to this regimen
- People with a negative sputum culture who in the judgment of the clinician likely represent paucibacillary or low mycobacterial burden TB disease unless the person is included in one of the non-recommended groups

Current Challenges with Supply of Rifampin

- There are ongoing issues with the supply of Rifampin:
 - IDOH/Purdue Pharmacy have obtained some supply from the Emergency Stockpile and from a neighboring jurisdiction for patients who were on therapy with Rifampin as part of their TB treatment regimen (at the time the supply issue arose) to continue to remain on Rifampin.
 - **Rifabutin should be used in place of Rifampin in the 4-drug regimen (RIPE) for new patients with TB disease.**
 - Any patients needing therapy for **LTBI** should be prescribed the **3HP** regimen containing Isoniazid and Rifapentine or **mono therapy with Isoniazid**.
 - Rifabutin is not recommended to be used to treat LTBI due to the Rifampin shortage at this time.

Thank You!

Questions?

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Appendices

Intensive Phase			Continuation Phase					
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Abbreviations: RPT= rifapentine; MOX= Moxifloxacin; INH = isoniazid; PZA = pyrazinamide

^aMust be administered completely within 70 days from treatment initiation. If this target is not met, the patient should be considered to have interrupted therapy and should be managed as described in [TB treatment guidelines](#) .

^bAt least 5 of 7 weekly doses should be administered under direct observation. Directly observed therapy means that a healthcare worker watches the TB patient swallow each dose of the prescribed drugs. The healthcare worker should ask the patient how he or she is feeling, check the medications before they are taken, ask the patient if he or she is experiencing any side effects, and answer any questions the patient may have. Where local policies, allow, eDOT has been shown to be an acceptable alternative to traditional DOT. Contact your [state or local TB control office](#) for more information about eDOT policies and procedures.

^cMust be administered within 84 days from intensive phase completion. If this target is not met, the patient should be considered to have interrupted therapy and should be managed as described in [TB treatment guidelines](#) .

^dPyridoxine (vitamin B6), 25–50 mg/day, should be given with isoniazid to all patients.

^eDrugs are administered with food once a day, every day of the week.

Four-month TB Treatment Regimen Table

Source:
<https://www.cdc.gov/tb/topic/treatment/tbdisease.htm>

Considerations for Specific Groups of People with TB Disease, continued

CDC **recommends** that **clinical consultation** be obtained to determine if the 4-month rifapentine-moxifloxacin regimen is an acceptable treatment option for:

- People at increased risk of Mycobacterium tuberculosis (*M. tuberculosis*) resistance to any drug in the 4-month regimen
- People who received more than 5 doses of TB treatment in the prior 6 months
- People who received more than 5 doses of latent TB infection treatment in the prior 6 months
- People who received more than 5 doses of treatment with any one or more of the following drugs for any reason (e.g., urinary tract infection, pneumonia) in the prior 30 days:
 - Isoniazid (INH), rifampin (RIF), rifabutin, rifapentine (RPT), pyrazinamide (PZA), or any fluoroquinolone
- People who have serum or plasma alanine aminotransferase or aspartate aminotransferase more than 3 times the upper limit of normal or total bilirubin more than 2.5 times the upper limit of normal, or with preexisting advanced liver disease
- People who have renal insufficiency or end-stage renal disease, or
 - Serum or plasma creatinine level more than 2 times the upper limit of normal, or
 - Plasma potassium level less than 3.5 milliequivalents per liter (mEq/L)
- People who have types of extrapulmonary TB that are likely to be paucibacillary, not pose a substantial risk of death or disability, and not require prolonged treatment (i.e., pleural or lymph node TB)
- People with a sputum specimen that is unable to be submitted for any *M. tuberculosis* resistance testing prior to initiating the 4-month treatment regimen

Considerations for Specific Groups of People with TB Disease, continued

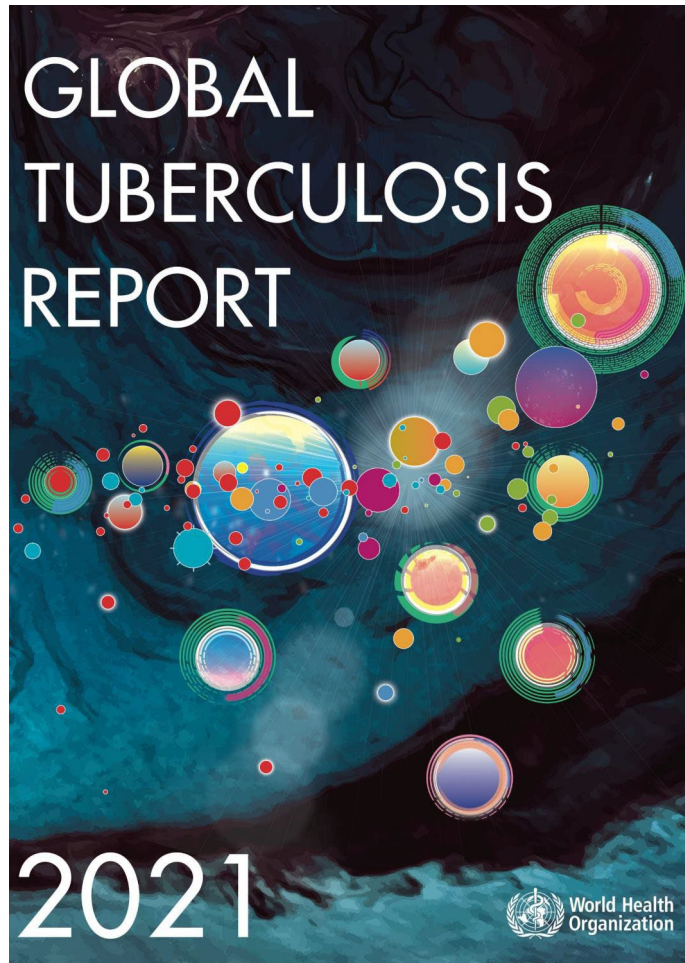
CDC **does not recommend** the 4-month rifapentine-moxifloxacin regimen for:

- People who are younger than 12 years old
- People with a body weight below 40 kilograms (kg)
- People who are pregnant or breastfeeding
- People who have most types of suspected or documented extrapulmonary TB
- People who have a history of prolonged QT syndrome or concurrent use of one or more QT-prolonging medications (in addition to moxifloxacin (MOX))
- People who are receiving medications with known clinically relevant drug-drug interactions with INH, RPT, PZA, or MOX
- People with a baseline *M. tuberculosis* isolate known or suspected to be resistant to RIF, INH, PZA, or any fluoroquinolone

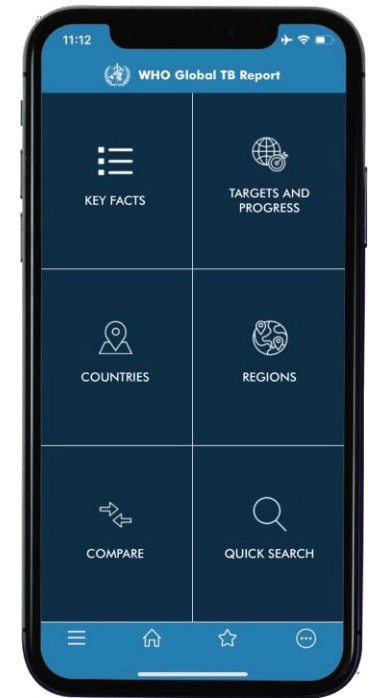
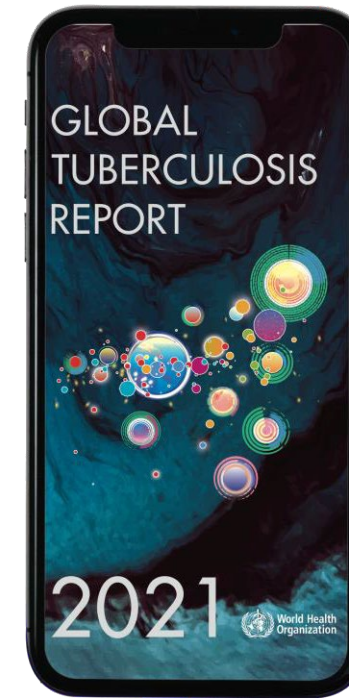
References

- <https://www.cdc.gov/tb/topic/treatment/tbdisease.htm> Accessed March 2022
- <https://www.cdc.gov/tb/topic/treatment/ltbi.htm> Accessed March 2022

For more information



Mobile app – country-specific as well as regional and global data for all key indicators



<https://www.who.int/publications/i/item/9789240037021>

<https://www.who.int/news/item/20-10-2020-who-2020-global-tb-report-app-now-available-in-english-french-and-russian>